REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims.

In the present Reply, claims 2, 3, 9, 10, 16, 17, 22, 25, 28, 29, 30, 37, 38 and 42 have been amended. Claims 5, 12, 19, 24, 27, 31 and 32 were previously canceled without prejudice or disclaimer of the subject matter contained therein. Also, claims 44-63 have been added. Thus, claims 1-4, 6-11, 13-18, 20-23, 25, 26, 28-30 and 33-63 are pending in this application.

No new matter has been added by way of the amendments to the present specification and pending claims. One of skill in the art would understand that typographical errors are being corrected in the present specification. Further, upon reviewing a few sources (explained in more detail below), Applicants have discovered such typographical errors and are making the appropriate changes herein. Similar changes are made to claims 37-38. The amendments to claims 2, 3, 9, 10, 16, 17, 22, 25, 28, 29, 30, 37, 38 and 42 merely delete subject matter. Thus, no new matter has been added.

Further, no new matter has been added by way of new claims 44-63. Support for claims 44-53 is found in the present specification at, e.g., page 5, lines 1-6. Support for new claims 54-63 is found in the Examples and at, e.g., page 4, lines 11+.

Based upon the above considerations, entry of the present amendment is respectfully requested.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw the objection and all rejections and allow the currently pending claims.

Claim Objection Under 37 C.F.R. § 1.75

Claim 28 stands objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 22. Applicants respectfully traverse.

The Markush group of the acidic polysaccharide includes "carrageenan" in claim 22, and not in claim 28. Thus, Applicants respectfully submit that the claims are not duplicates of one another. Withdrawal of this objection is respectfully requested

Further, Applicants thank the Examiner for the reminder of the misspellings present in some of the pending claims. In this regard, Applicants have reviewed *The Merck Index* (2001) for the appropriate spellings of some of the drugs listed in claims 37 and 38, as well as in the present specification. Since these changes have been made herein, Applicants respectfully request the Examiner to consider Applicants' changes. Applicants are further attaching excerpts from the mentioned sources that show the correct spellings of the various medicines.

Issues Under 35 U.S.C. § 112, Second Paragraph

Claims 3, 10 and 17 stand rejected under 35 U.S.C. § 112, second paragraph, for asserted reasons of indefiniteness. Applicants respectfully traverse and respectfully refer the Examiner to the scope of the claims as presented herein. The disputed language no longer appears in these claims. Thus, withdrawal of this rejection is respectfully requested.

Issues under 35 U.S.C. § 102(b) & § 102(e)

Claims 1-3, 7-10, 14-17, 21 and 43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Drug Information for Vantin® (Physician's Desk Reference (1995); newly cited; hereinafter "Drug Information").

Claims 1-2, 6-9, 13-16, 20-22, 25, 28-30 and 39-43 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Diehl (U.S. Patent No. 5,612,026; also newly cited; hereinafter "Diehl '026").

Applicants respectfully traverse, and reconsideration and withdrawal of these rejections are respectfully requested.

Applicants note that the previous rejections have been overcome, and that the instant rejections are new (see page 7 of the Office Action as well).

Distinctions over the Drug Information reference

The present invention is directed to a basic medicine and acidic polysaccharide being in a medicinal composition, where these ingredients are in intimate contact in order to form an electric interaction and thus prevent the basic medicine from dissolving in saliva. Such features are missing in the cited Drug Information reference. Specifically, the Examiner refers to, in part, the ingredients of cefpodoxim and carrageenan described in the Drug Information reference. However, any use of carrageenan in Drug Information is in the oral suspension (and not in, e.g., a tablet). When used in an oral suspension, as disclosed in the cited reference, carrageenan is a dispersing agent or a gelling agent. In other words, when suspended in water, there is no prevention of the unpleasant taste of the basic medicine as instantly claimed. Further, Drug Information does not disclose the claimed electric interaction.

Thus, Applicants respectfully submit that this rejection has been overcome since "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or

inherently described, in a single prior art reference." *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants further note that the mentioned claimed features are not discussed in the Office Action. Thus, because of the lack of disclosure of all features as instantly claimed (e.g., electric interaction; prevention of the unpleasant taste of the medicine), the rejection in view of Drug Information is overcome.

Further, Applicants respectfully submit that the Drug Information reference further fails to disclose a tablet containing carrageenan. An oral suspension is merely described, which does not prevent the unpleasant taste of the basic medicine. In this regard, Applicants respectfully refer the Examiner to the scope of new claims 54-63.

Also, with regard to the disputed method claims (e.g., instantly pending claim 8), there is no disclosure in Drug Information of mixing or blending the claimed ingredients. Instead, the Drug Information reference merely discloses an oral suspension that contains (not mixes) a medicine and agents. In addition, Drug Information does not disclose the claimed electric interaction. Thus, the rejection of the pending method claims is overcome for these additional reasons.

Accordingly, in light of the above comments, reconsideration and withdrawal of this rejection under § 102(b) are respectfully requested.

Distinctions over the Diehl '026 reference

The cited Diehl '026 reference merely describes an anion-exchanging resin with xanthan gum. Still, there is no description in Diehl '026 of the claimed electric interaction. Further, xanthan gum is deleted from the claims. Thus, this rejection has been overcome. Reconsideration and withdrawal of this rejection are respectfully requested.

Issues Under 35 U.S.C. § 103(a)

Claims 3-4, 10-11, 17-18, 23, 26 and 35-38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Diehl '026 in view of Drug Information. Further, claims 1-4, 6-11, 13-18, 20-23, 25-26, 28-30 and 33-43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Tai (U.S. Patent No. 5,013,557; hereinafter "Tai '557"). Applicants respectfully traverse both rejections, and reconsideration and withdrawal thereof are respectfully requested.

Distinctions over the Combination of Diehl '026 & Drug Information

As mentioned, the cited primary reference of Diehl '026 merely describes an anion-exchanging resin with xanthan gum and fails to describe or suggest the claimed electric interaction. Further, xanthan gum is deleted from the claims.

Also as mentioned, the cited secondary reference of Drug Information merely describes using carrageenan as a dispersing or gelling agent in an oral suspension (and not in, e.g., a tablet). Drug Information fails to disclose any prevention of the unpleasant taste of the basic medicine, and/or the electric interaction as instantly claimed. The present invention is patentably distinct in that upon oral administration, the electric interaction is produced which masks the bitter taste of the basic medicine.

Thus, even when combined (whether appropriate or not), the cited combination fails to disclose, e.g., the claimed electric interaction. Therefore, a *prima facie* case of obviousness has not been established since there is no disclosure of all claimed features, even when Diehl '026 is combined with the Drug Information reference. *See In re Vaeck*, 947 F.2d, 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *see also In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Accordingly, this rejection has been overcome.

Applicants also submit that the requisite motivation is missing. The Examiner refers to how it would be obvious to the skilled artisan "to have substituted one basic active agent for the other in order to benefit from the masking properties for more medications with unpleasant taste" (at page 5 of the Office Action). Diehl '026 focuses on liquid (drink mix) compositions using xanthan gum for reducing serum cholesterol levels (see Abstract; Col. 2, lines 26+). In this regard, replacing the key or essential xanthum gum in Diehl '026 with another polysaccharide gum or ingredient would destroy the intended function of Diehl '026. Applicants note that if a proposal for modifying the cited reference in an effort to attain the claimed invention causes the reference to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. *See In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Since the asserted combination of Diehl '026 and the secondary reference of Drug Information means the alteration of key ingredient(s) in the primary reference of Diehl '026, Applicants respectfully submit that the requisite motivation is lacking and that this rejection has been overcome.

The same reasoning of destroying the intended function of the primary reference applies if another medicine (e.g., donepezil) replaces the key medicine in Diehl '026 (e.g., cholestyramine), in

that Diehl '026 is directed to reducing serum cholesterol levels. Applicants respectfully submit that the cited combination is improper for this additional reason.

Applicants further note that no technical evidence has been cited or provided in the Office Action to show that the skilled artisan would stray away from the objective of Diehl '026 directed to reducing serum cholesterol level, or that the basic medicine in Diehl '026 should or could be appropriately replaced. The Diehl '026 reference is directed to "Cholesterol Lowering Drink Mix Compositions" (see title of patent), wherein Drug Information is directed to a specific antibiotic. One of skill in the art, in reviewing a reference mainly directed to reducing serum cholesterol levels, would not refer to a reference that discusses antibiotics. Thus, Applicants respectfully submit that the requisite motivation is lacking for this additional reason. *In re Vaeck*.

Applicants even submit that the two cited references are not in an analogous field of one another. *In re Oetiker*, 24 USPQ2d 1443 (Fed. Cir. 1992) (the reference(s) "must either be in the field of the applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned" (24 USPQ2d at 1445; citing *In re Deminski*, 230 USPQ 313, 315 (Fed. Cir. 1986)). Given the many medical references, Applicants respectfully submit that the same field of endeavor cannot be so

broadly classified to include a reference directed to treating cholesterol, and another reference directed to a description of an antibiotic.

Further, the requisite reasonable expectation of success is lacking since "Obviousness requires one of ordinary skill in the art have a reasonable expectation of success as to the invention—'obvious to try' and 'absolute predictability' are incorrect standards." *Velander v. Garner*, 68, USPQ2d 1769, 1784 (Fed. Cir. 2003) (citing *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988)). In this regard, Applicants respectfully submit that the asserted combination means any reference broadly or generically describing a medicine could be combined. However, such a reasoning equals an "obvious to try" rationale and is improper for an analysis of patentability under § 103(a). *See In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (CAFC 1988) (In *In re* Fine, the CAFC reversed the BPAI by stating: "The Board reiterated the Examiner's bald assertion that 'substitution of one type of detector for another in the system of Eads would have been within the skill of the art,' *but neither of them offered any support for or explanation of this conclusion.*") (emphasis added); *see also In re Deuel*, 34 USPQ2d 1210, 1216 (CAFC 1995) (where the court states: "Obvious to try" has long been held not to constitute obviousness. A general incentive does not make obvious a

particular result, nor does the existence of techniques by which those efforts can be carried out") (citing *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-1681 (CAFC 1988)). Accordingly, Applicants respectfully submit that this rejection is improper for this reason as well, wherein the reasonable expectation of success is lacking.

Based on the above comments, reconsideration and withdrawal of this rejection are respectfully requested.

Distinctions over the Modification of Tai '557

The Office Actions states that although Tai '557 does not exemplify compositions containing a basic medicine and an acidic polysaccharide, that Tai '557 does "teach mixing a medicine with unpleasant taste with a polysaccharide such as carrageenan to mask the taste..." (see page 6, second paragraph of the Office Action).

The cited Tai '557 reference shows a spraying-dried product including sucralfate (see Abstract; Col. 4, lines 59+; see also the various claims in the reference). More specifically, it is seen in the Tai '557 reference that the unpleasant taste-masking action is caused by a matrix imposed on microcapsules (B), referred to in column 5 or in its claim 9 at column 25. The matrix (B) includes sugar alcohols as a bulking sweet agent (claim 15), and a hydrophobic lubricating agent (see, e.g., claim 1). The spraying-

dried product delivers the medicine component slowly in the mouth out of the outer layer because of the hydrophobic lubricating agent. Thus, the (sweet) bulking agent is delivered in the mouth before the medicine component, which masks the unpleasant taste of the medicine component. This is not the present invention as claimed.

In the present invention, upon oral administration, the electric interaction is produced which masks the bitter taste of the basic medicine. The cited Tai '557 reference fails to show the combination of the instantly claimed invention, as well as the claimed electric interaction.

Further, though the Office Action mentions how Tai '557 fails to exemplify compositions containing a basic medicine and an acidic polysaccharide, Applicants submit that this is the instantly claimed composition and that this is a significant deficiency of the Tai '557 reference. *In re Vaeck*.

Applicants also submit that the requisite motivation in order to the achieve the present invention is lacking, as claimed, since features such as the claimed electric interaction is not seen or suggested anywhere in disclosure of Tai '557. Thus, Applicants respectfully submit that the instantly claimed compositions are patentably distinct from the spraying-dried product of Tai '557.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eugene T. Perez (Reg. No. 48,501) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petition for a three (3) month extension of time for filing a response in connection with the present application. The required fee of $1020.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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0425-0736P

Attachments:
- Excerpts from *The Merck Index* (2001)

THE
MERCK INDEX

AN ENCYCLOPEDIA OF
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2001

***d*-Form.** Crystals from petr ether, mp 136.5-137.5° (sintering). $[\alpha]_D^{23}$ +98.9° (methanol).

***l*-Form.** Crystals from petr ether, mp 136.5-137.5° (sintering). $[\alpha]_D^{23}$ −101.9° (methanol).

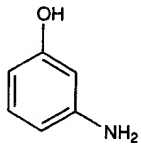
***dl*-Form hydrochloride.** $C_{19}H_{24}N_2O.HCl$. Slightly deliquescent leaflets from alcohol + ether, dec 190-191°. Bitter taste. Soluble in water, alcohol. A 1% aq soln has a pH of 6.8. LD_{50} in mice (mg/kg): 34.7 i.v.; 396 orally (Cazort).

***dl*-Form acid sulfate.** Centrine. $C_{19}H_{24}N_2O.H_2SO_4$; mol wt 394.49. Deliquescent crystals from isopropanol + ethyl acetate, mp 185-187°. The commercial medicinal grade, mp 178-181°. Bitter taste. uv max (1% H_2SO_4): 258.5 nm ($A_{1cm}^{1\%}$ 10.3); min: 249 nm. Freely sol in water, alc. Very slightly sol in chloroform. Practically insol in ether. pH of 2.5% aq soln 1.3-2.2.

THERAP CAT: Antispasmodic.

THERAP CAT (VET): Antispasmodic; antiemetic.

459. *m*-Aminophenol. [591-27-5] 3-Amino-1-hydroxybenzene; 3-hydroxyaniline. C_6H_7NO; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Manuf by reduction of *m*-nitrophenol: Freifelder, Robinson, **US 3079435** (1963 to Abbott). Toxicity study: Koelzer, Giesen, *Z. Naturforsch.* **6b,** 183 (1951).



Crystals, mp 122-123°. Sol in 40 parts cold water, freely in hot water, alcohol, ether, amyl alcohol; slightly in benzene, very slightly in petr ether. LD_{50} i.p. in mice: 4.5 mg/20g (Koelzer, Giesen).

USE: Dye intermediate, manuf *p*-aminosalicylic acid.

460. *o*-Aminophenol. [95-55-6] 2-Aminophenol; 2-amino-1-hydroxybenzene; 2-hydroxyaniline. C_6H_7NO; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Manuf by reduction of *o*-nitrophenol: Freifelder, Robinson, **US 3079435** (1963 to Abbott).

Crystals, rapidly becoming brown, mp 170-174°; sublimes. One gram dissolves in 50 ml cold water, 23 ml alcohol; freely soluble in ether, very slightly in benzene. *Keep tightly closed and protected from light.*

Hydrochloride. $C_6H_7NO.HCl$. Crystals readily becoming gray on exposure to light. Freely sol in water or alcohol.

USE: Manuf azo and sulfur dyes; dyeing furs and hair. Hydrochloride used in dyeing fur, hair, leather, etc.

461. *p*-Aminophenol. [123-30-8] *p*-Hydroxyaniline; 4-amino-1-hydroxybenzene; Azol; Rodinal; Unal; Ursol P. C_6H_7NO; mol wt 109.13. C 66.04%, H 6.47%, N 12.83%, O 14.66%. Usually prepd by the reduction of *p*-nitrophenol: *BIOS Final Report* **986;** Freifelder, Robinson, **US 3079435** (1963 to Abbott).

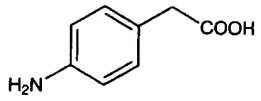
Orthorhombic plates from water. *Deteriorates under the influence of air and light.* mp 189.6-190.2°. The commercial product is usually pink, mp 186°. Can be sublimed at 0.3 mm and 110° without decompn. bp_{760} 284° (decompn); $bp_{8.0}$ 167°; $bp_{3.0}$ 150°; $bp_{0.3}$ 130.2°. Kb at 15° = 6.6×10^{-9}. Forms salts with acids and bases. Soly in water: 0.39% at 13°; 0.65% at 24°; 0.80% at 30°; 1.5% at 50°; 4.7% at 80°; 8.5% at 96°. Soly in ethyl methyl ketone: 9.3% at 58.5°; in abs ethanol: 4.5% at 0°. Practically insol in benzene, chloroform.

Hydrochloride. $C_6H_7NO.HCl$. Cryst powder; gradually becomes darker. Decomp about 306°. Very sol in water; sol in alc.

Caution: May cause skin sensitization, dermatitis. Inhalation can cause asthma, methemoglobin formation.

USE: Photographic developer; intermediate in the manufacture of sulfur and azo dyes; in dyeing furs and feathers.

462. *p*-Aminophenylacetic Acid. [1197-55-3] 4-Aminobenzeneacetic acid; *p*-amino-α-toluic acid. $C_8H_9NO_2$; mol wt 151.16. C 63.57%, H 6.00%, N 9.27%, O 21.17%. Prepd by the reduction of *p*-nitrophenylacetic acid with hydrogen sulfide in the presence of ammonia: G. R. Robertson, *Org. Syn.* **coll. vol. I,** 52 (2nd ed., 1941).



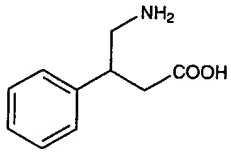
Plates, leaflets from water, mp 199-200° (dec). Moderately sol in hot water; sol in alcohol, in alkalies.

Hydrochloride. $C_8H_9NO_2.HCl$. Rods from HCl, freely sol in water, sol in alcohol (about 3% w/w).

Ethyl ester. $C_{10}H_{13}NO_2$. Platelets from water, mp 51°.

***N*-Benzoyl deriv.** Needles from alcohol, mp 205-206°.

463. 4-Amino-3-phenylbutyric Acid. [1078-21-3] β-(Aminomethyl)benzenepropanoic acid; β-(aminomethyl)hydrocinnamic acid; 4-amino-3-phenylbutanoic acid; β-phenyl-γ-aminobutyric acid; phenygam; PhGABA; Phenigam; Fenigam; Phenigama; Fenigama. $C_{10}H_{13}NO_2$; mol wt 179.22. C 67.02%, H 7.31%, N 7.82%, O 17.85%. Prepn starting with α,γ-diamino-β-phenylpropane: Jackson, Kenner, *J. Chem. Soc.* **1928,** 1657. Alternate prepn: Cologne, Pouchol, *Bull. Soc. Chim. France* **1962,** 598. Pharmacology: R. A. Khaunina, *Bull. Exp. Biol. Med.* **57,** 52 (1964). Structure-activity studies: *idem, Farmakol. Toksikol.* **31,** 202 (1968). Activity studies of the isomers: *eidem, Byull. Eksp. Biol. Med.* **72,** 49 (1971), *C.A.* **76,** 81208t (1972).



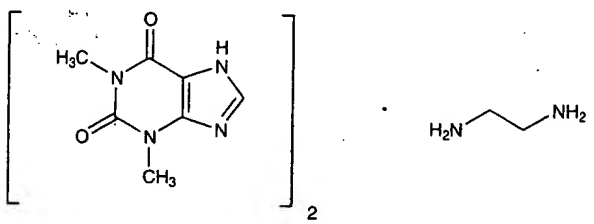
mp 250-253° (dec).

Hydrobromide. [103095-38-1] $C_{10}H_{13}NO_2.HBr$. Irregular platelets from benzene, mp 114°.

Hydrochloride. [3060-41-1] LD_{50} in mice, rats (mg/kg): 900, 700 i.p. (Khaunina, 1964).

THERAP CAT: Mood elevator, tranquilizer.

464. Aminophylline. [317-34-0] 3,7-Dihydro-1,3-dimethyl-1*H*-purine-2,6-dione compd with 1,2-ethanediamine (2:1); theophylline compd with ethylenediamine; theophylline ethylenediamine; theophyllamine; Afonilum; Aminodur; Cardophylin; Euphyllina; Pecram; Phyllocontin; Phyllotemp; Planphylline; Pulmovet; Tefamin. $C_{16}H_{24}N_{10}O_4$; mol wt 420.43. C 45.71%, H 5.75%, N 33.32%, O 15.22%. Prepn: Grüter, **US 919161** (1909 to Byk). Toxicity data: C. R. Thompson, M. R. Warren, *J. Lab. Clin. Med.* **31,** 1337 (1946). Comprehensive description: K. D. Thakker, L. T. Grady, *Anal. Profiles Drug Subs.* **11,** 1-44 (1982). Reviews of clinical experience: J. A. Stirt, S. F. Sullivan, *Anesth. Analg.* **60,** 587-602 (1981); A. G. Perry, *AACN Clin. Issues* **6,** 297-306 (1995).



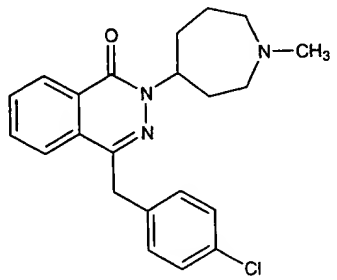
Occurs as the dihydrate. White or slightly yellowish granules or powder. Slight ammoniacal odor. Bitter taste. Gradually absorbs carbon dioxide from the air and becomes incompletely sol due to liberation of theophylline. One gram dissolves in about 5 ml water, but the soln may become turbid on standing.

Monoclinic prismatic needles, mp 106.5°. Distills above 360° with partial anhydride formation. bp_{100} 286.5°; bp_{50} 265°; bp_{15} 237°; bp_{10} 225°. $d_4^{110.6}$ 1.0291. One liter of water dissolves 1.0 g at 1.0°; 2.4 g at 20°; 8.2 g at 50°; 22 g at 65°. Freely sol in boiling water, in alcohol. 1000 g of ether dissolves 18.8 g at 11° and 26.8 g at 15°. pK_1 (25°) 4.53; pK_2 5.33.

Dimethyl ester. $C_{11}H_{20}O_4$. Liquid, d_4^{20} 1.0026. mp −3.9°. bp_8 140°.

THERAP CAT: Antiacne.

909. Azelastine. [58581-89-8] 4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone; 4-(*p*-chlorobenzyl)-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone; 4-(*p*-chlorobenzyl)-2-(*N*-methylperhydroazepin-4-yl)-1(2*H*)-phthalazinone. $C_{22}H_{24}ClN_3O$; mol wt 381.91. C 69.19%, H 6.33%, Cl 9.28%, N 11.00%, O 4.19%. Orally active H_1-histamine receptor antagonist. Prepn: **BE 778269**; D. Vogelsang *et al.*, **US 3813384** (1972, 1974 both to Asta-Werke AG). Synthesis and x-ray structure determn: G. Scheffler *et al.*, *Arch. Pharm.* **321,** 205 (1988). Pharmacology: K. Tasaka, M. Akagi, *Arzneimittel- Forsch.* **29,** 488 (1979). Pharmacology and toxicology: H. J. Zechel *et al.*, *ibid.* **31,** 1184 (1981). Series of articles on pharmacokinetics, pharmacology and toxicology: *ibid.* 1184-1238. Mechanism of action studies: N. Chand *et al.*, *Int. J. Immunopharmacol.* **7,** 833 (1985); *eidem*, *Br. J. Pharmacol.* **87,** 443 (1986). HPLC determn in plasma: J. Pivonka *et al.*, *J. Chromatog.* **420,** 89 (1987). Clinical evaluations in asthma: H. Magnussen, *Chest* **91,** 855 (1987); M. K. Albazzaz, K. R. Patel, *Thorax* **43,** 306 (1988).



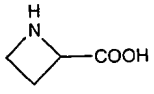
Oil. Sol in methylene chloride.

Monohydrate. $C_{22}H_{24}ClN_3O.H_2O$. Crystals from alcohol/water. Two distinct crystal forms have been identified (Scheffler).

Hydrochloride. [79307-93-0] A-5610; E-0659; W-2979M; Allergodil; Astelin; Azeptin; Optilast; Rhinolast. $C_{22}H_{24}ClN_3O.HCl$; mol wt 418.37. Crystals from alcohol, mp 225-229°. LD_{50} in male, female mice, male, female rats (mg/kg): 36.5, 35.5, 26.9, 30.3 i.v.; 56.4, 42.8, 43.2, 46.6 i.p.; 63.0, 54.2, 66.5, 59.6 s.c.; 124, 139, 310, 417 orally (Zechel).

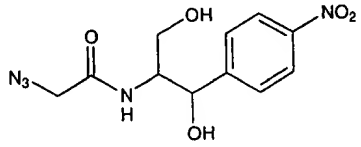
THERAP CAT: Antihistaminic.

910. 2-Azetidinecarboxylic Acid. [2517-04-6] $C_4H_7NO_2$; mol wt 101.10. C 47.52%, H 6.98%, N 13.85%, O 31.65%. From *Convallaria majalis* L. (lily-of-the-valley) and *Polygonatum officinale* Moensh., *Liliaceae:* Fowden, *Biochem. J.* **64,** 323 (1956); Fowden, Bryant, *ibid.* **70,** 626 (1958). Structure: Virtanen, *Angew. Chem.* **67,** 619 (1955); Fowden, *loc. cit.* Biosynthesis: Linko, *Acta Chem. Scand.* **12,** 101 (1958); Fowden, Bryant, *Biochem. J.* **71,** 210 (1959); Fowden, *ibid.* **71,** 643 (1959); Leete, *J. Am. Chem. Soc.* **86,** 3162 (1964). Shows growth-inhibitory activity on cultures of *Escherichia coli* and on germinating seeds of different species in which it does not normally occur; Fowden, Richmond, *Biochim. Biophys. Acta* **71,** 459 (1963). Acts as a proline analog where a stoichiometric replacement of proline occurred with production of abnormal proteins having impaired biological activity: Peterson, Fowden, *Nature* **200,** 148 (1963).



Crystals from 95% hot methanol, discolors at 200° and c ens until 310° when heating stopped. $[\alpha]_D^{20}$ −108° (c = Unstable to mineral acids. Soluble in cold and hot water. I tically insol in abs ethanol.

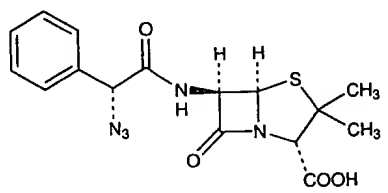
911. Azidamfenicol. [13838-08-9] 2-Azido-*N*-[2 droxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamid (−)-*threo*-1-*p*-nitrophenyl-2-azidoacetylaminopropan 3-diol; D-(−)-*threo*-2-azidoacetamido-1-*p*-nitrophenyl-1,3 panediol; azidoamphenicol; Berlicetin; Leukomycin-N; Pos icol; Thilocanfol. $C_{11}H_{13}N_5O_5$; mol wt 295.25. C 44.75 4.44%, N 23.72%, O 27.09%. Semi-synthetic antibiotic re to chloramphenicol, *q.v.* Prepn: Meiser, Domagk, **US 288** (1959 to Bayer).



Crystals from ethylene chloride, mp 107°. $[\alpha]_D^{20}$ −20° 1.6 in ethyl acetate). pH 7.1. Sol in water up to 2%.

THERAP CAT: Antibacterial.

912. Azidocillin. [17243-38-8] (2*S*,5*R*,6*R*)-6-[[(2*R* dophenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-az clo[3.2.0]heptane-2-carboxylic acid; α-azidobenzylpen 6-[D-α-azidophenylacetamido]penicillanic acid; SPC-97D; 2351. $C_{16}H_{17}N_5O_4S$; mol wt 375.41. C 51.19%, H 4.5 18.66%, O 17.05%, S 8.54%. Semi-synthetic antibiotic to penicillin. Prepn: B. O. H. Sjöberg, B. A. Ekström **940488**; *eidem*, **US 3293242** (1963, 1966 to Beecham); El *et al.*, *Acta Chem. Scand.* **19,** 281 (1965). Pharmacology: sen *et al.*, *Antimicrob. Ag. Chemother.* **1967,** 568; Tu Frisk, *ibid.* 573. Chemistry: Sjöberg *et al.*, *ibid.* 560. Me studies: Ramsey *et al.*, *Arzneimittel-Forsch.* **22,** 1962 (1

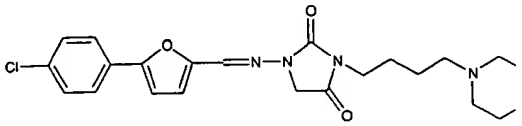


Sodium salt. [35334-12-4] Globacillin; Longatren; lin. $C_{16}H_{16}N_5NaO_4S$; mol wt 397.39.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antimicrobial. (In mastitis, as fe plement).

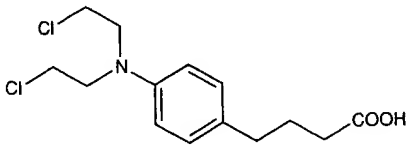
913. Azimilide. [149908-53-2] 1-[[[5-(4-Chl nyl)-2-furanyl]methylene]amino]-3-[4-(4-meth perazinyl)butyl]-2,4-imidazolidinedione. $C_{23}H_{28}ClN_5$(wt 457.96. C 60.32%, H 6.16%, Cl 7.74%, N 15. 10.48%. Potassium channel blocker. Prepn: S. S. Pelo **WO 93 04061** (1993 to Procter & Gamble); C.-N. Yu *e* **5462940** (1995 to Norwich Eaton). Clinical pharmaco A. Corey *et al.*, *J. Clin. Pharmacol.* **37,** 946 (1997). trial to improve post-infarct survival: A. J. Camm *et al* *Cardiol.* **81,** Suppl. 6A, 35D (1998). Review of electr logic properties and pharmacology: R. Karam *et al.*, *ib* 46D.



Dihydrochloride. [149888-94-8] NE-10064; Stedi $H_{28}ClN_5O_3.2HCl$; mol wt 530.88. Crystals from ethar

THERAP CAT: Antiarrhythmic (class III).

C. J. Ross, *Biochem. Pharmacol.* **13,** 969 (1964). Review of carcinogenicity studies: *IARC Monographs* **9,** 125-134 (1975). Comprehensive description: M. Tariq, A. A. Al-Badr, *Anal. Profiles Drug Subs.* **16,** 85-118 (1987).



Flattened needles from petr ether, mp 64-66°. Sol in ether. Sol at 20° in 1.5 parts alcohol, in 2.5 parts chloroform, in 2 parts acetone. Practically insol in water. LD_{50} i.p. in rats: 58.2 μmole/kg (Ross).

Note: This substance has been listed as a known human carcinogen: *Ninth Report on Carcinogens* (PB2000-107509, 2000) p III-21.

THERAP CAT: Antineoplastic.

THERAP CAT (VET): Antineoplastic agent, esp for leukemia.

2084. Chloramine-B. [127-52-6] *N*-Chlorobenzenesulfonamide sodium salt; (*N*-chlorobenzenesulfonamido)sodium; sodium benzenesulfochloramine; Neomagnol. $C_6H_5ClNNaO_2S$; mol wt 213.62. C 33.74%, H 2.36%, Cl 16.60%, N 6.56%, Na 10.76%, O 14.98%, S 15.01%. $C_6H_5SO_2NNaCl$. Prepd via benzenesulfonamide: Chattaway, *J. Chem. Soc.* **87,** 145 (1905); Cuiban *et al., Pharmazie* **13,** 407 (1958).

Trihydrate. Prisms. Soluble in 20 parts of water, more sol in hot water. Sol in 25 parts of ethanol, yielding a turbid soln. Very sparingly sol in ether, chloroform. An aq soln first turns red litmus paper blue, then gradually bleaches it. Gives a red color wth phenolphthalein.

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antiseptic (topical).

2085. Chloramine-T. [127-65-1] *N*-Chloro-4-methylbenzenesulfonamide sodium salt; (*N*-chloro-*p*-toluenesulfonamido)sodium; sodium *p*-toluenesulfonchloramide; chloramine; Aktiven; Chloraseptine; Chlorazene; Chlorazone; Euclorina; Gansil; Halamid; Mianine; Tochlorine; Tolamine. $C_7H_7ClNNaO_2S$; mol wt 227.65. C 36.93%, H 3.10%, Cl 15.57%, N 6.15%, Na 10.10%, O 14.06%, S 14.09%. *p*-$CH_3C_6H_4SO_2NNaCl$. Prepd via *p*-toluenesulfonamide: Chattaway, *J. Chem. Soc.* **87,** 145 (1905); Inglis, *J. Soc. Chem. Ind. (London)* **37,** 288 (1918); F. J. Welcher, *Organic Analytical Reagents* **vol. 4** (Van Nostrand, New York, 1948) pp 316-320.

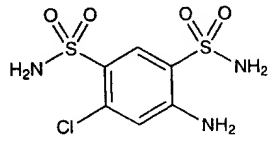
Trihydrate. Prisms. Loses water on drying. Dec slowly on exposure to air. *Keep well closed.* Fairly sol in water. Practically insol in benzene, chloroform, ether. Dec by alc.

USE: Detection of bromate and halogens, F. J. Welcher, *loc. cit.*

THERAP CAT: Antibacterial.

THERAP CAT (VET): Antiseptic (topical).

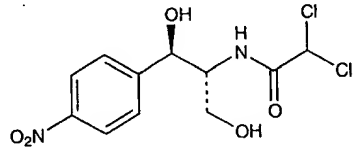
2086. Chloraminophenamide. [121-30-2] 4-Amino-6-chloro-1,3-benzenedisulfonamide; 4-amino-6-chloro-*m*-benzenedisulfonamide; 5-chloro-2,4-bis(sulfonamido)aniline; 6-amino-4-chlorobenzene-1,3-disulfonamide; 5-chloro-2,4-disulfamylaniline; Idorese. $C_6H_8ClN_3O_4S_2$; mol wt 285.73. C 25.22%, H 2.82%, Cl 12.41%, N 14.71%, O 22.40%, S 22.44%. Prepn: Novello, Sprague, *J. Am. Chem. Soc.* **79,** 2028 (1957); Novello, **US 2809194**; **US 2965655**; **US 2965656** (1957, 1960, 1960 all to Merck & Co.); Novello *et al., J. Org. Chem.* **25,** 965 (1960).



Crystals from aq ethanol, mp 251-252°. uv max (ethanol): 223.5-224.5, 265-266, 312-314 nm (ε 41776, 18633, 3874). Slightly sol in water; more freely sol in alkalies.

THERAP CAT: Diuretic.

2087. Chloramphenicol. [56-75-7] 2,2-Dichloro-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamide; D-*threo*-*N*-dichloroacetyl-1-*p*-nitrophenyl-2-amino-1,3-propanediol; D(−)-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol; D-*threo*-*N*-(1,1′-dihydroxy-1-*p*-nitrophenylisopropyl)dichloroacetamide; Ak-Chlor; Amphicol; Anacetin; Aquamycetin; Chemicetina; Chloramex; Chlorasol; Chloricol; Chlorocid; Chloromycetin; Chloroptic; Cloramfen; Clorocyn; Enicol; Farmicetina; Fenicol; Intramycetin; Kemicetine; Leukomycin; Micoclorina; Mychel; Mycinol; Novomycetin; Ophthochlor; Pantovernil; Paraxin; Quemicetina; Ronphenil; Sintomicetina; Sno Phenicol; Synthomycetin; Tevcocin; Tifomycine; Veticol; Viceton. $C_{11}H_{12}Cl_2N_2O_5$; mol wt 323.13. C 40.89%, H 3.74%, Cl 21.94%, N 8.67%, O 24.76%. Broad spectrum antibiotic obtained from cultures of the soil bacterium *Streptomyces venezuelae:* Bartz, *J. Biol. Chem.* **172,** 445 (1948); Gottlieb *et al., J. Bact.* **55,** 409 (1948); Ehrlich *et al., ibid.* **56,** 467 (1948). Isol from the moon snail, *Lunatia heros:* C. A. Price *et al., J. Antibiot.* **34,** 118 (1981). Structure: Rebstock *et al., J. Am. Chem. Soc.* **71,** 2458 (1949). Synthesis: Controulis *et al., ibid.* 2465; Long, Troutman, *ibid.* 2469, 2473. *See also* **US 2483871**; **US 2483884**; **US 2483892.** Alternate synthesis: Ehrhart *et al., Ber.* **90,** 2088 (1957); **GB 795131**; **GB 796901** *C.A.* **53,** 2161 (1959) (both to Chinoin); **US 2839577** (1958 to Chinoin). Review and evaluation of toxicity studies: *IARC Monographs* **10,** 85-9 (1976). Review of pharmacology and clinical efficacy: Shalit, M. I. Marks, *Drugs* **28,** 281-291 (1984). Comprehensive description: D. Szulczewski, F. Eng, *Anal. Profiles Drug Subs.* **4,** 47-90 (1975); A. A. Al-Badr, H. A. El-Obeid, *ibid.* **15,** 707-760 (1986). *Reviews:* Hahn in *Antibiotics,* **vol. 1,** D. Gottlieb, P. D. Shaw, Eds. (Springer-Verlag, New York, 1967) pp 307-330; Pestka, *ibid.* **vol. 3,** J. W. Corcoran, F. E. Hahn, Eds. (1975) pp 370-395; O. Pongs, *ibid.* **vol. 5,** pt. 1, F. E. Hahn, Ed. (1979) pp 26-42.



Needles or elongated plates from water or ethylene dichloride, mp 150.5-151.5°. Sublimes in high vacuum. $[\alpha]_D^{27}$ +18.6° (c = 4.86 in ethanol). $[\alpha]_D^{25}$ −25.5° (ethyl acetate). uv max: 278 nm ($E_{1cm}^{1\%}$ 298). Soly (25°) in water: 2.5 mg/ml; in propylene glycol 150.8 mg/ml. Very sol in methanol, ethanol, butanol, ethyl acetate, acetone. Fairly sol in ether. Insol in benzene, petr ether, vegetable oils. Soly in 50% acetamide soln about 5%. Additional soly data: Weiss *et al., Antibiot. Chemother.* **7,** (1957). Aq solns are neutral. Neutral and acid solns are stable on heating.

Monosuccinate sodium salt. [982-57-0] Globenicol; Isophenicol. $C_{15}H_{15}Cl_2N_2NaO_8$; mol wt 445.19. Freely sol in water (about 50% w/w).

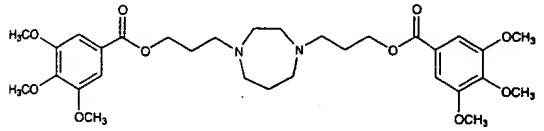
Palmitate. [530-43-8] Chlorambon; Chloropal; Cloroxina. Prepn: Edgerton, **US 2662906** (1953 to Parke, Davis). Structure: Edgerton *et al., J. Am. Chem. Soc.* **77,** 27 (1955). Description: Glazko *et al., Antibiot. Chemother.* **2,** 234 (1952). Soly data: Weiss *et al., ibid.* **7,** 374 (1957). Crystals from benzene, mp 90°. Practically tasteless. $[\alpha]_D^{26}$ +24.6° (c = 5 in ethanol). uv max (ethanol): 271 nm ($E_{1cm}^{1\%}$ 179). Very slightly sol in water (1.05 mg/ml at 28°); petr ether (0.225 mg/ml). Freely sol in methanol, ethanol, chloroform, ether, benzene.

Monosuccinate arginine salt. [34327-18-9] Chloramphenicol arginine succinate; Paraxin Succinate A. $C_{21}H_{30}Cl_2N_4$; mol wt 597.41. mp 135-145° (dec.). *See Japan. Med.* **7**(10), 15 (1970).

Pantothenate calcium complex (4:1). [31342-36-6] Chloramphenicol pantothenate; Pantofenicol. $C_{62}H_{80}CaCl_8N_{10}$

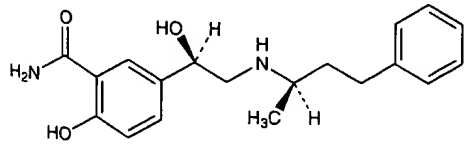
Sodium salt. Dikegulac-sodium; Ro-7-6145; Atrinal. C_{12}-$_7NaO_7$; mol wt 296.25. Powder, mp >300°. Vapor pressure 25°: $<10^{-10}$ mm Hg. Soly at 20° (g/l): water 590; methanol 0; ethanol 230; chloroform 60; acetone <10; hexane <10; clohexanone <10. LD_{50} in mice, male, female rats (mg/kg): 500, 31000, 18000 orally; LC_{50} (96 hr) in bluegill sunfish, nbow trout (ppm): >10000, >5000 (de Silva).
USE: Plant growth regulator; herbicide.

3223. Dilazep. [35898-87-4] 3,4,5-Trimethoxybenzoic acid rahydro-1*H*-1,4-diazepine-1,4(5*H*)-diyl)di-3,1-propanediyl es- 3,4,5-trimethoxybenzoic acid diester with tetrahydro-1*H*-1,4-zepine-1,4(5*H*)-dipropanol; 1,4-bis[3-(3,4,5-trimethoxybenzoyl-)propyl]perhydro-1,4-diazepine; *N,N'*-bis[3-(3,4,5-trimethoxy-nzoyloxy)propyl]homopiperazine; *N,N'*-(bis-ω-hydroxypropyl)-nopiperazine 3,4,5-trimethoxybenzoate (diester). $C_{31}H_{44}N_2O_{10}$; l wt 604.69. C 61.57%, H 7.33%, N 4.63%, O 26.46%. pn: **GB 1107470** corresp to Arnold *et al.*, **US 3532685** 68, 1970 both to Asta-Werke). Series of articles on phar-cology and metabolism: *Arzneimittel-Forsch.* **22,** 639-666 72). Toxicology: H. H. Abel *et al., ibid.* 667. Clinical re-s: Messerich, *Med. Welt.* **1972,** 563.



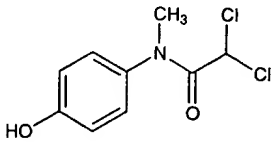
lihydrochloride. [20153-98-4] Asta C 4898; Comelian; melian; Labitan. $C_{31}H_{44}N_2O_{10}.2HCl$; mol wt 677.62. Crys- from ethanol, mp 194-198° (monohydrate). LD_{50} in male e, male rats (mg/kg): 26.6, 19.1 i.v.; 161, 90.1 i.p.; 3740, 150 orally (Abel).
HERAP CAT: Vasodilator (coronary).

3224. Dilevalol. [75659-07-3] 2-Hydroxy-5-[(1*R*)-1-hy-xy-2-[[(1*R*)-1-methyl-3-phenylpropyl]amino]ethyl]benz-de; *(R,R)*-labetalol; Sch-19927; Dilevalon; Levadil; Uni-l. $C_{19}H_{24}N_2O_3$; mol wt 328.40. C 69.49%, H 7.37%, N 3%, O 14.62%. Non-selective β-adrenergic blocker with odilating activity; active isomer of labetalol, *q.v.* For prepn acemate *see* labetalol. Synthesis and preliminary pharma-gy: J. E. Clifton *et al., J. Med. Chem.* **25,** 670 (1982); E. Gold *et al., ibid.* 1363. Absolute configuration: P. Murray-t *et al., Acta Crystallogr.* **C40,** 825 (1984). Adrenoceptor cking properties in comparison with labetalol: E. J. Sybertz l., *J. Pharmacol. Exp. Ther.* **218,** 435 (1981). Antihyperten-: and hemodynamic effects in rats and dogs: T. Baum *et al.,* l. 444; and cardiac effects: J. J. Lynch *et al., ibid.* **239,** 719 86). HPLC determn in biological fluids: K. B. Alton *et al., Chromatog.* **425,** 363 (1988). Clinical evaluation in hyper-sion: J. Soberman *et al., J. Clin. Hypertens.* **3,** 271 (1987);). Wallin *et al., Arch. Intern. Med.* **148,** 534 (1988). Sym-ium on pharmacology and clinical efficacy: *J. Cardiovasc. rmacol.* **11,** Suppl. 2, S1-S45 (1988).



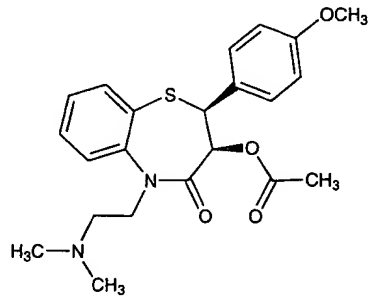
ium. $[\alpha]_D$ −21.7°.
lydrochloride. [75659-08-4] $C_{19}H_{24}N_2O_3.HCl$. Polymor-c crystals from ethanol, mp 133-134° (dec); mp 192-193.5° c). $[\alpha]_D^{26}$ −30.6° (c = 1.0 in ethanol).
HERAP CAT: Antihypertensive.

3225. Diloxanide. [579-38-4] 2,2-Dichloro-*N*-(4-hydroxy-nyl)-*N*-methylacetamide; 2,2-dichloro-4'-hydroxy-*N*-methyl-lanilide; *N*-dichloroacet-4-hydroxy-*N*-methylanilide; 4-hy-xy-*N*-methyldichloroacetanilide; Entamide. $C_9H_9Cl_2NO_2$; mol wt 234.08. C 46.18%, H 3.88%, Cl 30.29%, N 5.98%, O 13.67%. Prepn: P. Oxley *et al.,* **US 2912438** (1959 to Boots Pure Drug). Spectrophotometric determn in 2-component tablet formulation: S. M. Galal *et al., J. Pharm. Belg.* **46,** 315 (1991). Clinical trial of combination with metronidazole, *q.v.*, in amoebiasis and giardiasis: H. Qureshi *et al., J. Int. Med. Res.* **25,** 167 (1997). Review of clinical experience: J. B. McAuley *et al., Clin. Infect. Dis.* **15,** 464-468 (1992).

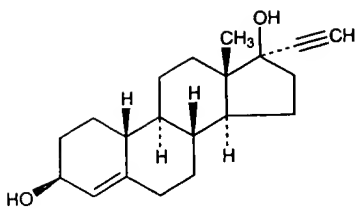


Crystals from ethyl acetate, mp 175°.
Furoate. [3736-81-0] Diloxanide 2-furoic acid ester; Furamide.
THERAP CAT: Antiamebic.

3226. Diltiazem. [42399-41-7] (2*S-cis*)-3-(Acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,-5-benzothiazepin-4(5*H*)-one; (+)-*cis*-5-[2-(dimethylamino)eth-yl]-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzo-thiazepin-4(5*H*)-one acetate (ester). $C_{22}H_{26}N_2O_4S$; mol wt 414.53. C 63.74%, H 6.32%, N 6.76%, O 15.44%, S 7.74%. Calcium channel blocker with vasodilating activity. Prepn (un-spec stereochem): H. Kugita *et al.,* **DE 1805714**; *eidem,* **US 3562257** (1969, 1971 both to Tanabe Seiyaku); *eidem, Chem. Pharm. Bull.* **19,** 595 (1971). Resolution of optical isomers: H. Inoue *et al., Yakugaku Zasshi* **93,** 729 (1973), *C.A.* **79,** 66331w (1974). Stereospecific synthesis: K. Igarashi, T. Honma, **DE 3415035**; *eidem,* **US 4552695** (1984, 1985 both to Shionogi). Structure-activity studies: Sato *et al., Arzneimittel-Forsch.* **21,** 1338 (1971); T. Nagao *et al., Chem. Pharm. Bull.* **21,** 92 (1973). Pharmacology and toxicity: *eidem, Japan. J. Pharmacol.* **22,** 467 (1972). Metabolism: Meshi *et al., Chem. Pharm. Bull.* **19,** 1546 (1971). Review of synthesis and pharmacology: H. Inoue, T. Nagao, *Chron. Drug Discovery* **3,** 207-238 (1993). Comprehensive description: D. J. Mazzo *et al., Anal. Profiles Drug Subs. Excip.* **23,** 53-98 (1994). Review of pharmacology and efficacy in angina: M. Chaffman, R. N. Brogden, *Drugs* **29,** 387-454 (1985); in hypertension: M. R. Weir, *J. Clin. Pharmacol.* **35,** 220-232 (1995). Comparative clinical trial in prevention of complications of hypertension: L. Hansson *et al., Lancet* **356,** 359 (2000).



Hydrochloride. [33286-22-5] CRD-401; Adizem; Altiazem; Angizem; Britiazim; Bruzem; Cardizem; Citizem; Deltazen; Dilacor XR; Diladel; Dilpral; Dilrene; Dilzem; Dilzene; Herbesser; Masdil; Tiazac; Tildiem; Zilden. $C_{22}H_{26}N_2O_4S.HCl$; mol wt 450.99. Fine needles from ethanol-isopropanol, mp 207.5-212°. Odorless, with a bitter taste. $[\alpha]_D^{24}$ +98.3 ± 1.4° (c = 1.002 in methanol). Freely sol in water, methanol, chloroform, formic acid; slightly sol in abs ethanol. Practically insol in benzene. Insol in ether. LD_{50} in male, female mice, male, female rats (mg/kg): 61, 58, 38, 39 i.v.; 260, 280, 520, 550 s.c.; 740, 640, 560, 610 orally (Nagao, 1972).
THERAP CAT: Antianginal; antihypertensive; antiarrhythmic (class IV).



Diacetate. [297-76-7] 3β,17β-Diacetoxy-17α-ethynyl-4-estrene; SC-11800; Femulen; Luteonorm; Luto-Metrodiol; Metrodiol. $C_{24}H_{32}O_4$; mol wt 384.51. Crystals from methanol + water, mp ~ 126-127°. $[\alpha]_D$ −72.5° (chloroform).

Diacetate mixture with mestranol. Luteolas; Metrulen; Ovaras; Ovulen.

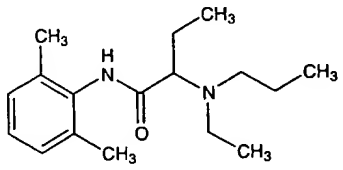
Diacetate mixture with ethinyl estradiol. Conova; Demulen; Miniluteolas.

THERAP CAT: Progestogen; in combination with estrogen as oral contraceptive.

3892. Ethynylbenzene. [536-74-3] Phenylacetylene. C_8H_6; mol wt 102.13. C 94.08%, H 5.92%. $C_6H_5C{\equiv}CH$. Prepd by dropping β-bromostyrene on molten potassium hydroxide and distilling: Hessler, *Org. Syn.* **2,** 67 (1922).

Liquid. d_4^{20} 0.9300. mp −44.8°. bp_{760} 142.4°; bp_{90} 75°; bp_{15} 39°. n_D^{20} 1.5489. Insol in water; miscible with alcohol, ether, other organic solvents.

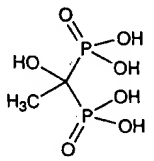
3893. Etidocaine. [36637-18-0] *N*-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide; 2-(ethylpropylamino)-2′,6′-butyroxylidide. $C_{17}H_{28}N_2O$; mol wt 276.42. C 73.87%, H 10.21%, N 10.13%, O 5.79%. Prepn: H. J. F. Adams *et al.*, **DE 2162744**; *eidem*, **US 3812147** (1972, 1974 both to Astra). Activity and toxicity studies: *eidem, J. Pharm. Sci.* **61,** 1829 (1972).



Hydrochloride. [36637-19-1] W-19053; Duranest. $C_{17}H_{28}N_2O.HCl$; mol wt 312.89. Crystals from abs ethanol-ether and isopropanol-isopropylether, mp 203-203.5°. LD_{50} in female mice (mg/kg): 6.7 i.v.; 99 s.c. (Adams, 1972).

THERAP CAT: Anesthetic (local).

3894. Etidronic Acid. [2809-21-4] (1-Hydroxyethylidene)bisphosphonic acid; (1-hydroxyethylidene)diphosphonic acid; ethane-1-hydroxy-1,1-diphosphonic acid; Dequest 2010; Fostex P. $C_2H_8O_7P_2$; mol wt 206.03. C 11.66%, H 3.91%, O 54.36%, P 30.07%. Bisphosphonate antiresorptive agent. Prepn: H. von Baeyer, K. A. Hofmann, *Ber.* **30,** 1973 (1897); and characterization of the acid and disodium salt: F. Kasparek, *Monatsh.* **99,** 2016 (1968); B. Blaser *et al., Z. Anorg. Allgem. Chem.* **381,** 247 (1971). Use as detergent builder: F. L. Diehl, **US 3159581** (1964 to Proctor & Gamble). Determn in pharmaceutical formulations: E. W. Tsai *et al., J. Pharm. Biomed. Anal.* **11,** 513 (1993). Symposium on clinical efficacy in malignancy-related hypercalcemia: *Am. J. Med.* **82,** Suppl 2A, 1-78 (1987). Review of pharmacology and therapeutic efficacy in resorptive bone disease: C. J. Dunn *et al., Drugs Aging* **5,** 446-474 (1994); of clinical safety and efficacy in osteoporosis: T. P. van Staa *et al., Pharmacotherapy* **18,** 1121-1128 (1998).



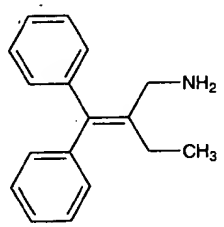
Crystallizes from water as the monohydrate. pK_1 1.35 ±0.08; pK_2 2.87 ±0.01; pK_3 7.03 ±0.01; pK_4 11.3. Very sol in water (69% at 20° C). Insol in acetic acid.

Disodium salt. [7414-83-7] Disodium dihydrogen (1-hydroxyethylidene)bis[phosphonate]; etidronate disodium; Didronel; Diphos; Etidron. $C_2H_6Na_2O_7P_2$; mol wt 249.99. Crystallizes from water as the di- or tetrahydrate.

USE: Sequestering and chelating agent; scale and corrosion inhibitor.

THERAP CAT: Bone resorption inhibitor.

3895. Etifelmin. [341-00-4] 2-Diphenylmethylenebutylamine; 2-ethyl-3,3-diphenyl-2-propenylamine; EDPA; Na III. $C_{17}H_{19}N$; mol wt 237.34. C 86.03%, H 8.07%, N 5.90%. Prepn: Heinrich, Heiger, **DE 1122514** (1962 to Giulini GmbH), *C.A.* **57,** 733c (1962).

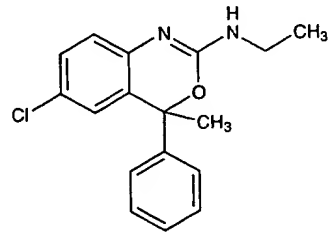


Hydrochloride. [1146-95-8] Tensinase D. $C_{17}H_{19}N.HCl$; mol wt 273.81. Crystals, mp 232°. Freely sol in water.

Mixture of hydrochloride and nicotinate. Gilutensin.

THERAP CAT: CNS stimulant; antihypotensive.

3896. Etifoxine. [21715-46-8] 6-Chloro-*N*-ethyl-4-methyl-4-phenyl-4*H*-3,1-benzoxazin-2-amine; 6-chloro-2-(ethylamino)-4-methyl-4-phenyl-4*H*-3,1-benzoxazine; HOE-36801. $C_{17}H_{17}ClN_2O$; mol wt 300.79. C 67.88%, H 5.70%, Cl 11.79%, N 9.31%, O 5.32%. Psychotropic agent with anxiolytic and anticonvulsant activity. Prepn: **FR M7358**; H. Kuch *et al.*, **US 3725404** (1969, 1973 both to Hoechst); I. Hoffmann *et al., Arzneimittel-Forsch.* **20,** 975 (1970). Exptl psychopharmacological study: J. R. Boissier *et al., Therapie* **27,** 325 (1972). Analysis of EEG effects: D. Bente *et al., Arzneimittel-Forsch.* **25,** 944 (1975). Evaluation of psychotropic effect: R. Corsico *et al., Psychopharmacologia* **45,** 301 (1976).



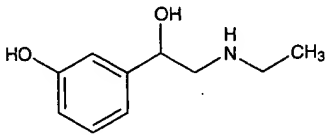
Colorless crystals from petr ether, mp 90-92°. uv max (ethanol): 273 nm (ε 21200). LD_{50} orally in mice: 12 g/kg (Hoffmann).

Hydrochloride. [56776-32-0] Stresam. $C_{17}H_{17}ClN_2O.HCl$; mol wt 337.25. Crystals, mp 150-151°.

THERAP CAT: Anxiolytic.

3897. Etilefrin. [709-55-7] α-[(Ethylamino)methyl]-3-hydroxybenzenemethanol; α-[(ethylamino)methyl]-*m*-hydroxybenzyl alcohol; *m*-hydroxy-α-(ethylaminomethyl)benzyl alcohol; α-(*m*-hydroxyphenyl)-β-(ethylamino)ethanol; ethylphenylephrine; etiladrianol. $C_{10}H_{15}NO_2$; mol wt 181.23. C 66.27%, H 8.34%, N 7.73%, O 17.66%. Sympathomimetic amine. Prepn: T. Goto, *J. Pharm. Soc. Japan* **74,** 318 (1954), *C.A.* **49,** 3960 (1955); **ES 273595** (1962 to Labs. Fher S.A.), *C.A.* **60,** 1649e (1964). Clinical pharmacology: A. J. Coleman *et al., Eur. J. Clin. Pharmacol.* **8,** 41 (1975). Clinical pharmacokinetics and disposition: J. H. Hengstmann *et al., ibid.* **9,** 179 (1975). HPLC determn in plasma: K. Kojima *et al., J. Chro-*

matog. **525,** 210 (1990). Clinical trial in arterial hypotension: T. Taivainen, *Acta Anaesthesiol. Scand.* **35,** 164 (1991); in neurocardiogenic syncope: F. Ammirati *et al., Am. J. Cardiol.* **86,** 472 (2000).



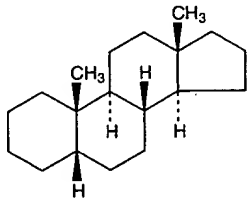
Crystals, mp 147-148°.

Hydrochloride. [534-87-2] Cardanat; Circupon; Effontil; Effortil; Efortil; Kertasin; Thomasin. $C_{10}H_{15}NO_2.HCl$; mol wt 217.70. Crystals, mp 121°. Bitter taste. Freely sol in water; sol in alcohol. Practically insol in chloroform.

THERAP CAT: Antihypotensive.

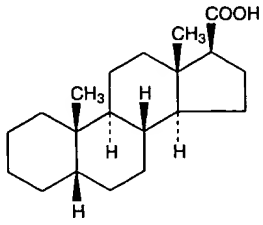
THERAP CAT (VET): Antihypotensive.

3898. Etiocholane. [438-23-3] (5β)-Androstane; 5-epiandrostane. $C_{19}H_{32}$; mol wt 260.46. C 87.62%, H 12.38%. Parent compd of alkyl substituted etiocholanes, such as pregnane, cholane, coprostane. Prepd from etiocholane-17-one semicarbazone: Butenandt, Dannenbaum, *Z. Physiol. Chem.* **229,** 192 (1934).



Needles from acetone, mp 78-80°.

3899. Etiocholanic Acid. [438-08-4] (5β,17β)-Androstane-17-carboxylic acid; aetiocholanic acid; etianic acid; etiocholane-17β-carboxylic acid. $C_{20}H_{32}O_2$; mol wt 304.47. C 78.90%, H 10.59%, O 10.51%. Prepn: Wieland *et al., Z. Physiol. Chem.* **161,** 80 (1926); Jacobs, Elderfield, *J. Biol. Chem.* **108,** 497 (1935); Tschesche, *Ber.* **68,** 9 (1935); Steiger, Reichstein, *Helv. Chim. Acta* **21,** 841 (1938).

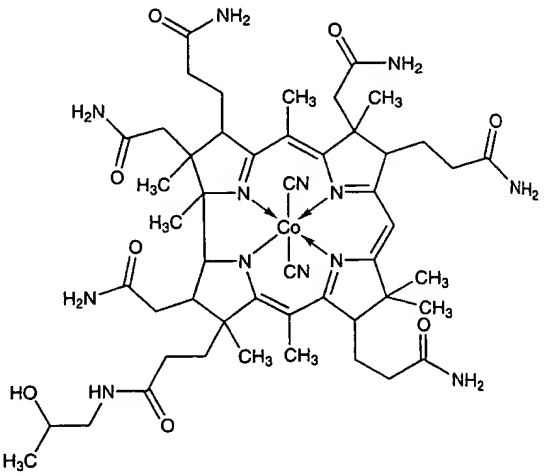


Needles from glacial acetic acid; elongated leaflets from acetic acid. Sublimes at 0.002 mm press. and 160° bath temp, mp 228-229°. Insol in water; sol in pentane.

Methyl ester. $C_{21}H_{34}O_2$. Needles from methanol, mp 99-101°.

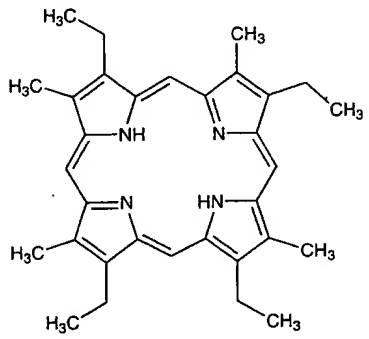
Note: The stem name "etianic acid" was proposed by the Subcommittee on Steroid Nomenclature of the National Research Council as a replacement for "etiocholanic acid" in order to avoid the use of the same name for parent hydrocarbons of different carbon content: *J. Am. Chem. Soc.* **74,** 2817 (1952).

3900. Etiocobalamin. [27792-36-5] Cobinamide dicyanide; vitamin B_{12p}; Factor B. $C_{50}H_{72}CoN_{13}O_8$; mol wt 1042.12. C 57.63%, H 6.96%, Co 5.66%, N 17.47%, O 12.28%. Vitamin B_{12} factor obtained by removal of the nucleotide from cyanocobalamin by acid hydrolysis. Isoln from calf feces: Ford, Porter, *Biochem. J.* **51,** V (1952). Prepn by acid hydrolysis: Gant *et al., ibid.* **56,** XXXIV (1954); Friedrich, Bernhauer, *Angew. Chem.* **65,** 627 (1953). Prepn from factor V_{1a} and D(−)-1-amino-2-propanol: Bernhauer *et al., Helv. Chim. Acta* **43,** (1960); Bernhauer, **US 3072674** (1963 to Hoffmann-La Roc



Note: The term etiocobalamin is used by some author designate any cobalamin lacking the nucleotide group pre in vitamin B_{12}.

3901. Etioporphyrin. [26608-34-4] 2,7,12,18-Tetra yl-3,8,13,17-tetramethyl-21*H*,23*H*-porphine; 1,3,5,8-tetram yl-2,4,6,7-tetraethylporphine; etioporphyrin III; mesoetio phyrin. $C_{32}H_{38}N_4$; mol wt 478.67. C 80.29%, H 8.00% 11.70%. Occurs in Bavarian oil shale, crude petr, ozoke amber, cannel coal and other hard varieties of bituminous c Treibs, *Ann.* **510,** 60 (1934); **517,** 184 (1935); *Angew. Ch* **49,** 682 (1936). Prepd by decarboxylation of mesoporphyrin Fischer, Treibs, *Ann.* **466,** 191, 206 (1928). Synthesis: Fisc Stangler, *Ann.* **462,** 265 (1928); Johnson *et al., J. Chem.* **1959,** 3416. Structure: Abraham *et al., ibid.* **1961,** 3468. *view:* Rimington, Kennedy, in M. Florkin, H. S. Mason, C *parative Biochemistry* (Academic Press, New York, 1962 557-614.



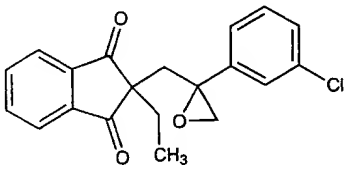
Long prismatic needles or butterflies from pyridine or chloroform-petr ether, mp 360-363°. pKa 18. Absorption 246, 269, 396, 497, 532, 566, 620, 645 nm (log ε 3.90, 5.22, 4.13, 3.99, 3.81, 3.65, 2.62).

Copper salt. $C_{32}H_{36}N_4Cu$. Red needles from pyridine-tic acid.

Magnesium salt. $C_{32}H_{36}N_4Mg$. Crystals from methan

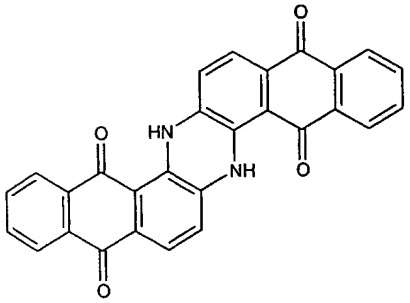
3902. Etiproston. [59619-81-7] (5*Z*)-7-[(1*R*,2*R*,3*R* 3,5-Dihydroxy-2-[(1*E*)-2-[2-(phenoxymethyl)-1,3-dioxola yl]ethenyl]cyclopentyl]-5-heptenoic acid; (5*Z*,13*E*)-(8*R* 11*R*,12*R*)-9,11-dihydroxy-15,15-ethylenedioxy-16-phen 17,18,19,20-tetranorprostadienoic acid; 15-deoxy-15,15-e enedioxy-16-phenoxy-17,18,19,20-tetranorprostaglandin Prostavet; Vetiprost. $C_{24}H_{32}O_7$; mol wt 432.51. C 66.65 7.46%, O 25.89%. Prostaglandin $F_{2\alpha}$ analog with estrus synchronizing activity. Prepn: W. Skuballa *et al.*, **DE 2434** *eidem,* **US 4088775** (1976, 1978 both to Schering AG);

ɔor pressure at 25°: 2.8×10^{-6} Pa. LD_{50} male, female rats g/kg): 631, 460 orally; >2000, >2000 dermally. LC_{50} in rats g/l): 1.57 by inhalation (Yagi).



JSE: Herbicide.

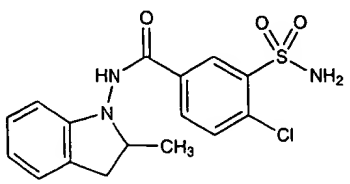
4959. Indanthrene®. [81-77-6] 6,15-Dihydro-5,9,14,18-thrazinetetrone; *N,N'*-dihydro-1,2,1',2'-anthraquinonazine. $_8H_{14}N_2O_4$; mol wt 442.42. C 76.01%, H 3.19%, N 6.33%, O .47%. Vat dye discovered by René Bohn (1901). Prepn: erz-David, Blangey, *Grundlegende Operationen der Farbenemie* (Vienna, 5th ed., 1943) pp 304-305; Thielert, Bauman, S 2693469 (1954 to Bayer); Sutter, Fioroni, **US 2831860** (1958 Ciba); Kastner, **US 3138612** (1964 to Allied Chem.). Structe: Weinstein, Merrit, *J. Am. Chem. Soc.* **81,** 3759 (1959).



Blue powder, dec 470-500°. uv max on cellophane film: 278 m. Practically insol in organic solvents. Sol in concd H_2SO_4, n dil alkali solns. ***Indanthrene Blue R***, the usual commercial rade, is extremely stable to light and heat, but sensitive to chlorine. A purer grade, which is not as sensitive to chlorine, is sold is ***Indanthrene Brilliant Blue FF***.

USE: Mainly to dye cotton.

4960. Indapamide. [26807-65-8] 3-(Aminosulfonyl)-4-chloro-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)benzamide; 4-chloro-*N*-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide; *N*-(3-sulfamyl-4-chlorobenzamido)-2-methylindoline; S-1520; SE-1520; Bajaten; Damide; Fludex; Indaflex; Indamol; Ipamix; Lozol; Natrilix; Noranat; Tandix; Veroxil. $C_{16}H_{16}ClN_3O_3S$; mol wt 365.84. C 52.53%, H 4.41%, Cl 9.69%, N 11.49%, O 13.12%, S 8.76%. Prepn: Beregi *et al.*, **FR 2003311**; *eidem*, US 3565911 (1969, 1971, both to Sci. Union et Cie, Soc. Franc. Recherche Med.). Pharmacology: Leary *et al., Curr. Ther. Res. Clin. Exp.* **15,** 571 (1973); D. B. Campbell, R. A. Moore, *Postgrad. Med. J., Suppl.* **57,** 7 (1981). Acute toxicity data: J. Kyncl *et al., Arzneimittel-Forsch.* **25,** 1491 (1975). Symposium on pharmacology and clinical efficacy: *Am. J. Med.* **84,** Suppl. 1B, 1-111 (1988); *Am. J. Cardiol.* **65,** Suppl. H, 1H-80H (1990). Comprehensive description: T. J. DiFeo, J. E. Shuster, *Anal. Profiles Drug Subs. Excip.* **23,** 229-268 (1994).

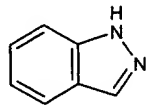


Crystals from isopropanol/water, mp 160-162°. uv max (methanol): 242, 278, 286 nm ($A^{1\%}_{1cm}$ 630, 98, 100). Sol in methanol, acetic acid, ethyl acetate. Very slightly sol in chloroform. pKa (25°) 8.8 ± 0.2. LD_{50} in rats, mice, guinea pigs (mg/kg): 393-421, 410-564, 347-416 i.p.; 394-440, 577-635, 272-358 i.v.; >3000 all species orally (Kyncl).

Hemihydrate. Pressural. $C_{16}H_{16}ClN_3O_3S.½H_2O$; mol wt 374.85.

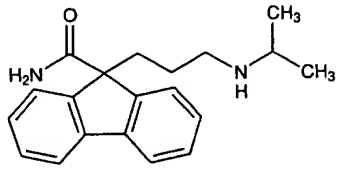
THERAP CAT: Antihypertensive; diuretic.

4961. 1*H*-Indazole. [271-44-3] Isoindazole; benzopyrazole. $C_7H_6N_2$; mol wt 118.14. C 71.17%, H 5.12%, N 23.71%. Prepn: Stephenson, *Org. Syn.*, **coll. vol. III,** 475 (1955); Ainsworth, *Org. Syn.* **39,** 27 (1959); Huisgen, Bast, *ibid.* **42,** 69 (1962).



Needles from hot water, mp 146.5°. bp_{743} 267-270°. Sol in hot water, alcohol, ether.

4962. Indecainide. [74517-78-5] 9-[3-[(1-Methylethyl)-amino]propyl]-9*H*-fluorene-9-carboxamide; 9-carbamoyl-9-(3-isopropylaminopropyl)fluorene; 9-[3-(isopropylamino)propyl]-9-(aminocarboyl)fluorene; ricainide. $C_{20}H_{24}N_2O$; mol wt 308.42. C 77.89%, H 7.84%, N 9.08%, O 5.19%. Prepn: W. B. Lacefield, R. L. Simon, **US 4197313** and **US 4452745** (1980, 1984 both to Lilly). Pharmacokinetics in animals: T. L. Lindstrom, G. W. Whitaker, *Drug Metab. Dispos.* **12,** 683 (1984). Metabolism: *eidem, ibid.* 691. LC determn in biological fluids: K. Z. Farid *et al., J. Chromatog.* **337,** 329 (1985). Toxicological studies: G. E. Sandusky, Jr., D. B. Meyers, *Fundam. Appl. Toxicol.* **5,** 175 (1985). Clinical evaluation in cardiac arrhythmias: P. F. Nestico *et al., Am. J. Cardiol.* **59,** 1332 (1987); P. J. Podrid *et al., ibid.* **61,** 764 (1988).

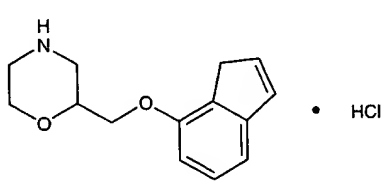


Crystals from Skelly B, mp 94-95°.

Hydrochloride. [73681-12-6] LY-135837; Decabid. $C_{20}H_{24}N_2O.HCl$; mol wt 344.89. Crystals from chloroform, mp 216.5-217°; also reported as crystals from fresh ethanol and diethyl ether, mp 203-204°. LD_{50} orally in male, female mice, rats: 100, 96, 103, 82 mg/kg (Sandusky, Meyers).

THERAP CAT: Antiarrhythmic (cardiac depressant).

4963. Indeloxazine Hydrochloride. [65043-22-3] 2-[(1*H*-Inden-7-yloxy)methyl]morpholine hydrochloride; (±)-2-[(7-indenyloxy)methyl]morpholine hydrochloride; YM-08054-1; Elen; Noin. $C_{14}H_{18}ClNO_2$; mol wt 267.76. C 62.80%, H 6.78%, Cl 13.24%, N 5.23%, O 11.95%. Serotonin uptake inhibitor. Prepn: M. Masuo *et al.*, **DE 2601703**; *eidem*, **US 4109088** (1976, 1978 both to Yamanouchi). Synthesis and resolution of isomers: T. Kojima *et al., Chem. Pharm. Bull.* **33,** 3766 (1985). Pharmacology and toxicity: S. Tachikawa *et al., Arch. Int. Pharmacodyn.* **238,** 81 (1979). Inhibition of synaptosomal uptake of serotonin and noradrenaline: M. Harada, H. Maeno, *Biochem. Pharmacol.* **28,** 2645 (1979). GLC determn in human plasma: A. G. Hayes, T. Chang, *J. Chromatog.* **272,** 176 (1983).

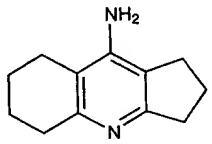


maceutical preparations by HPLC: D. A. Elvidge *et al., J. Chromatog.* **463,** 107 (1989). Review of distribution and chemistry of ipecac alkaloids: M.-M. Janot in *The Alkaloids,* **vol. 3,** R. H. F. Manske, H. L. Holmes, Eds. (Academic Press, New York, 1953) pp 363-394; A. Brossi, S. Teitel, *ibid.* **vol. 13,** 189-212 (1971). Review of use in acute poisoning: W. D. King, *Clin. Toxicol.* **17,** 353-358 (1980).

THERAP CAT: Emetic; expectorant.

THERAP CAT (VET): Emetic; expectorant.

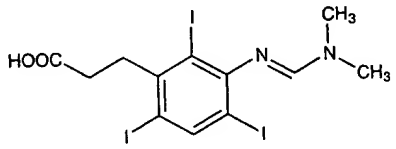
5089. Ipidacrine. [62732-44-9] 2,3,5,6,7,8-Hexahydro-1*H*-cyclopenta[*b*]quinolin-9-amine; 9-amino-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]quinoline; amiridin. $C_{12}H_{16}N_2$; mol wt 188.27. C 76.55%, H 8.57%, N 14.88%. Cholinesterase inhibitor; structural analog of tacrine, *q.v.* Prepn: A. V. Upadysheva *et al., Khim.-Farm. Zh.* **11,** 40 (1977), *C.A.* **86,** 189676q (1977). Prepn of the hydrochloride monohydrate: E. F. Levretskaya *et al.,* **DE 3231571**; *eidem,* **US 4550113** (1984, 1985 both to Sci. Res. Inst. Biol. Test. Chem. Compds). Neuropharmacology: T. Nabeshima *et al., Eur. J. Pharmacol.* **154,** 263 (1988). Anticholinesterase activity: S. Shibanoki *et al., Pharmacol. Biochem. Behav.* **39,** 499 (1991). Clinical evaluation in Alzheimer's disease: E. E. Bukatina *et al., Neurosci. Behav. Physiol.* **23,** 83 (1993).



Hydrochloride. [90043-86-0]; [118499-70-0] (monohydrate. NIK-247. $C_{12}H_{16}N_2.HCl$; mol wt 224.74. Prepd as the monohydrate. White or slightly creamy, odorless powder. Readily sol in water, dil acids; slowly sol in ethanol. Practically insol in acetone, ether, chloroform.

THERAP CAT: Nootropic.

5090. Ipodate. [5587-89-3] 3-[[(Dimethylamino)methylene]amino]-2,4,6-triiodobenzenepropanoic acid; 3-[(dimethylaminomethylene)amino]-2,4,6-triiodohydrocinnamicacid; 2,-4,6-triiodo-3-[(dimethylaminomethylene)amino]hydrocinnamic acid; β-(3-dimethylaminomethyleneamino-2,4,6-triiodophenyl)-propionic acid. $C_{12}H_{13}I_3N_2O_2$; mol wt 597.96. C 24.10%, H 2.19%, I 63.67%, N 4.68%, O 5.35%. Prepn: Priewe, Poljak, *Ber.* **93,** 2347 (1960). Toxicity data: J. O. Hoppe *et al., J. Med. Chem.* **13,** 997 (1970).



Crystals, mp 168-169° (dec 225°). Practically insol in water. Very sol in methanol, ethanol, chloroform, acetone, dil sulfuric acid. Estimated pK 5-5.5.

Sodium salt. [1221-56-3] Sodium ipodate; Biloptin; Oragrafin Sodium. $C_{12}H_{12}I_3N_2NaO_2$; mol wt 619.94. Bitter leaflets from water + acetone, mp 303-304° (decompn with evolution of iodine). Very freely sol in water; freely sol in methanol, ethanol. Practically insol in acetone, ether. Soly in DMF and DMSO about 33 g/100 ml; in dimethylacetamide about 66 g/100 ml. LD_{50} in mice (mg/kg): 290 i.v.; 2570 orally (Hoppe).

Calcium salt. [1151-11-7] Calcium ipodate; Solu-Biloptin; Oragrafin Calcium. $C_{24}H_{24}CaI_6N_4O_4$; mol wt 1233.98. Crystals, mp 298-302°. Soly in water at 20°: 0.1%. Sol in chloroform, dimethylformamide, hot propylene glycol.

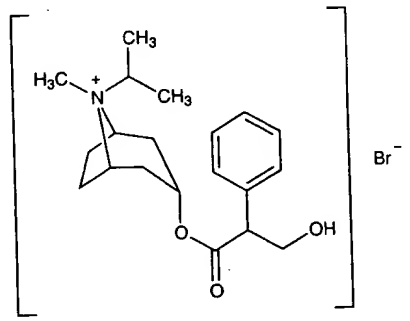
Ethyl ester. SH-617L. $C_{14}H_{17}I_3N_2O_2$; mol wt 626.01.

THERAP CAT: Diagnostic aid (radiopaque medium—cholecystographic).

5091. Ipomea. Mexican scammony (root); Orizaba jalap root. Dried root of *Ipomoea orizabensis* Ledenois, *Convolvulaceae.* Active constituent is the resin. Yields not less than 15% total ipomea resins. Different from *Ipomoea violacea* var. *Pearly Gates* Hort., *Convolvulaceae* and *Ipomoea rubrocoerulea* var. *praecox, morning-glory, ololiuqui,* which contain ergot alkaloids. Occurrence of lysergic acid derivatives and of ergolines in Ipomea: A. Hofmann, H. Tscherter, *Experientia* **16,** 414 (1960); D. Stauffacher *et al., Helv. Chim. Acta* **48,** 1379 (1965).

THERAP CAT: Cathartic.

5092. Ipratropium Bromide. [22254-24-6] (3-*endo*,8-*syn*)-3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide; 3α-hydroxy-8-isopropyl-1α*H*,5α*H*-tropanium bromide (±)-tropate; 8-isopropylnoratropine methobromide; *N*-isopropylnoratropinium bromomethylate; Sch-1000; Atem; Atrovent; Bitrop; Itrop; Narilet; Rinatec. $C_{20}H_{30}BrNO_3$; mol wt 412.37. C 58.25%, H 7.33%, Br 19.38%, N 3.40%, O 11.64%. Anticholinergic. Prepn: K. Zeile *et al.,* **ZA 67 07766**; *eidem,* **US 3505337** (1968, 1970, both to Boehringer, Ing.); W. Schulz *et al., Arzneimittel-Forsch.* **26,** 960 (1976). Chemistry and pharmacokinetics: W. Deckers, *Postgrad. Med. J.* **51,** Suppl. 7, 76 (1975). Pharmacology and toxicology: A. Engelhardt, H. Klupp, *ibid.* 82. Series of articles on pharmacology, toxicology, pharmacokinetics and clinical studies: *Arzneimittel-Forsch.* **26,** 974-985, 989-1020 (1976). Toxicity data: L. Sarafana *et al., ibid.* 985. *Review:* R. Bauer *et al.,* in *Pharmacological and Biochemical Properties of Drug Substances* **vol. 2,** M. E. Goldberg, Ed. (Am. Pharm. Assoc., Washington, DC, 1979) pp 489-515. Symposium on pharmacology, toxicology and clinical efficacy: *Am. J. Med.* **81**(5A), 1-102 (1986). Review of clinical toxicology: J. D. Truwit, *Crit. Care Clinics* **7,** 639-657 (1991).



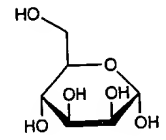
White crystals from *n*-propanol, mp 230-232°. Freely sol in water and lower alcohols. Insol in ether, chloroform and fluorohydrocarbons. Fairly stable in neutral and acid solns; rapidly hydrolyzed in alkaline soln. LD_{50} in male, female mice (mg/kg): 1001, 1083 orally; 12.29, 14.97 i.v.; 300, 340 s.c. LD_{50} in male, female rats (mg/kg): 1663, 1779 orally; 15.89, 15.70 i.v. (Sarafana).

THERAP CAT: Bronchodilator; antiarrhythmic.

5093. Ipriflavone. [35212-22-7] 7-(1-Methylethoxy)-3-phenyl-4*H*-1-benzopyran-4-one; 7-isopropoxy-3-phenyl-4*H*-1-benzopyran-4-one; 7-isopropoxy-3-phenylchromone; 7-isopropoxyisoflavone; FL-113; TC-80; Iprosten; Osten; Osteofix; Yambolap. $C_{18}H_{16}O_3$; mol wt 280.32. C 77.12%, H 5.75%, O 17.12%. Isoflavone derivative with anti-anginal and anti-osteopenic activity. Prepn: L. Feuer *et al.,* **DE 2125245** (1971 to Chinoin), *C.A.* **76,** 72407e (1972). Use as anabolic in animals: *eidem,* **US 3833730**; in humans; *eidem,* **US 3949085** (1974, 1976 both to Chinoin). Cardiovascular properties in stable angina: V. Grubich *et al., Lancet* **1,** 211 (1979). Cardiological effects in animals: L. Feuer *et al., Arzneimittel-Forsch.* **31,** 953 (1981). Metabolism and disposition in rats: K. Yoshida *et al., Radioisotopes* **34,** 612, 618 (1985). Effect in rats on estrogen-stimulated calcitonin secretion: I. Yamazaki, *Life Sci.* **38,** 757 (1986); I. Yamazaki, M. Kinoshita, *ibid.* 1535; on glucocorticoid-induced osteoporosis: I. Yamazaki *et al., ibid.* 951.

· sol in ethanol. Aq solns are mildly acidic and stable at
:mps. Claimed to be considerably less toxic than mech-
mine. LD_{50} i.v. in rats: 56 mg/kg (Scherf).
:AP CAT: Antineoplastic.

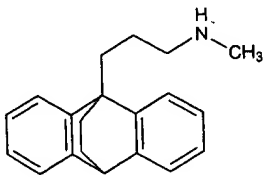
12. **D-Mannose.** [3458-28-4] Seminose; carubinose.
O_6; mol wt 180.16. C 40.00%, H 6.71%, O 53.28%.
of α-form by treating ivory nut shavings with H_2SO_4:
J. Res. Nat. Bur. Stand. **26,** 47 (1941); Isbell, Frush in
ıds in Carbohydrate Chemistry, R. L. Whistler, M. L. Wol-
Eds. (Academic Press, New York, 1962) pp 145-147.
and stability of α- and β-forms: Reeves, *J. Am. Chem.*
12, 1499 (1950); J. Sowden in *The Carbohydrates,* W. Pig-
Ed. (Academic Press, New York, 1957) pp 94-95.



α-D-Mannose

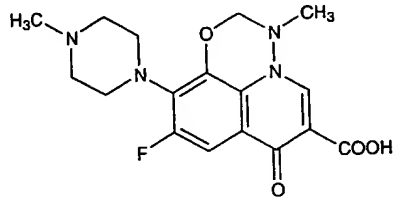
-Form. Crystals from methanol, mp 133°. $[\alpha]_D$ +29.3° →
1.2° (water).
-Form. Orthorhombic, bisphenoidal needles from alcohol
ıcetic acid, dec 132°. Sweet taste with bitter aftertaste. d^{20}
4. Shows mutarotation. $[\alpha]_D^{20}$ −17.0° → +14.2° (c = 4).
e gram dissolves in 0.4 ml water, 120 ml methanol, 250 ml
ethanol, 3.5 ml pyridine. pKa (18°): 11.98. Reduces Fehl-
's soln; is fermented by yeast.
Phenylhydrazone. $C_{12}H_{18}N_2O_5$. Crystals from dil ethanol,
199-200°. $[\alpha]_D^{20}$ +26.3° → +33.8° (pyridine).
$CaCl_2$-addition compd tetrahydrate. $C_6H_{12}O_6.CaCl_2.$-
H_2O. mp 101-102°. $[\alpha]_D^{20}$ −31.3° → +6.0° (c = 9).

5773. **Maprotiline.** [10262-69-8] *N*-Methyl-9,10-eth-
ıoanthracene-9(10*H*)-propanamine; 9-(γ-methylaminopropyl)-
10-dihydro-9,10-ethanoanthracene; 1-(3-methylaminopropyl)-
ibenzo[*b,e*]bicyclo[2.2.2]octadiene. $C_{20}H_{23}N$; mol wt 277.40.
86.59%, H 8.36%, N 5.05%. Prepn: P. Schmidt *et al.,* US
399201 (1968 to Ciba). Synthesis, NMR, mass spectra: M.
Vilhelm, P. Schmidt, *Helv. Chim. Acta* **52,** 1385 (1969). Tox-
city: R. Hess *et al., Boll. Chim. Farm.* **112,** 782 (1973), *C.A.*
81, 33479p (1974). Review of pharmacology and therapeutic
:fficacy: R. M. Pinder *et al., Drugs* **13,** 321 (1977). Compre-
hensive description: S. K. Suh, J. B. Smith, *Anal. Profiles Drug*
Subs. 15, 393-426 (1986).



mp 92-94°.
Hydrochloride. [10347-81-6] Ba-34276; Deprilept; Lu-
diomil; Psymion. $C_{20}H_{23}N.HCl$; mol wt 313.87. Crystals from
isopropanol, mp 230-232°. Freely sol in methanol and chloro-
form, slightly sol in water. Practically insol in isooctane. LD_{50}
in mice, rats (mg/kg): ~750, ~900 orally (Hess).
THERAP CAT: Antidepressant.

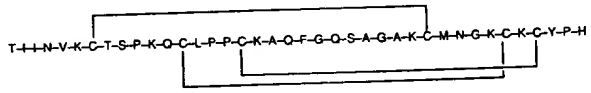
5774. **Marbofloxacin.** [115550-35-1] 9-Fluoro-2,3-dihy-
dro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido-
[3,2,1-*ij*][4,1,2]benzoxadiazine-6-carboxylic acid; Marbocyl.
$C_{17}H_{19}FN_4O_4$; mol wt 362.35. C 56.35%, H 5.28%, F 5.24%,
N 15.46%, O 17.66%. Fluorinated quinolone antibacterial.
Prepn: M. Aoki *et al.,* **EP 259804**; K. Yokose *et al.,* US
4801584 (1987, 1989 both to Hoffmann-LaRoche). HPLC de-
termn in plasma: M. A. Garcia *et al., J. Chromatog. B* **729,** 157
(1999). Evaluation of experimental surgical infection in dogs:
P. Gruet *et al., Vet. Rec.* **140,** 199 (1997). Pharmacokinetics and
efficacy in cattle: C. Eyett-Burton *et al., Cattle Practice* **5,** 289
(1997). Pharmacokinetics in renally impaired dogs: H. P. Le-
febvre *et al., J. Vet. Pharmacol. Ther.* **21,** 453 (1998).



Crystals from methanol, mp 268-269° (dec).
THERAP CAT (VET): Antibacterial.

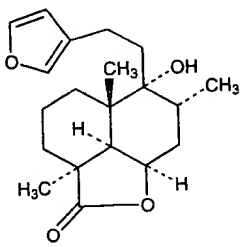
5775. Margaric Acid. [506-12-7] Heptadecanoic acid.
$C_{17}H_{34}O_2$; mol wt 270.45. C 75.50%, H 12.67%, O 11.83%.
$CH_3(CH_2)_{15}COOH$. Prepn: Kaufmann, Stamm, *Ber.* **91,** 2121
(1958); Bhattacharyya *et al., Chem. & Ind. (London)* **1959,**
1352; Hünig, Ledle, *Ber.* **93,** 913 (1960). Metabolism: Boyer,
Scheig, *Lipids* **4,** 615 (1969). Toxicity study: L. Orö, A.
Wretlind, *Acta Pharmacol. Toxicol.* **18,** 141 (1961).
Crystals from alcohol, mp 61°. d 0.853. bp_{100} 227°. n_D^{60}
1.4342. Insol in water. Freely sol in ether; slightly sol in al-
cohol. LD_{50} i.v. in mice: 360.3 mg/kg (Orö, Wretlind).

5776. Margatoxin. [145808-47-5] MgTX. $C_{178}H_{286}N_{52}$-
$O_{50}S_7$; mol wt 4179.02. C 51.16%, H 6.90%, N 17.43%, O
19.14%, S 5.37%. Peptide toxin isolated from the new world
scorpion, *Centruroides margaritatus,* consists of 39 amino acids
with 3 disulfide bridges. Selectively inhibits voltage-gated po-
tassium channels. Isoln and characterization: M. Garcia-Calvo
et al., J. Biol. Chem. **268,** 18866 (1993). Synthesis: M. A. Bed-
narek *et al., Biochem. Biophys. Res. Commun.* **198,** 619 (1994).
NMR determn of three dimensional structure: B. A. Johnson *et*
al., Biochemistry **33,** 15061 (1994). Use as an affinity label for
potassium channels: H.-G. Knaus *et al., ibid.* **34,** 13627 (1995);
H. S. Fischer, A. Saria, *Neurosci. Letters* **263,** 208 (1999).

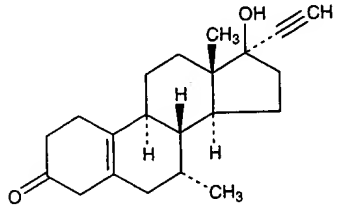


USE: Biochemical probe.

5777. Marrubiin. [465-92-9] [2a*S*-(2aα,5aβ,6α,7α,8aα,-
8bα)]-6-[2-(3-Furanyl)ethyl]decahydro-6-hydroxy-2a,5a,7-tri-
methyl-2*H*-naphtho[1,8-*bc*]furan-2-one; 15,16-epoxy-6β,9-di-
hydroxy-8β*H*-labda-13(16),14-dien-19-oic acid γ-lactone; 5-
[2-(3-furyl)ethyl]decahydro-5,8-dihydroxy-1,4a,6-trimethyl-1-
naphthoic acid γ-lactone. $C_{20}H_{28}O_4$; mol wt 332.43. C 72.26%,
H 8.49%, O 19.25%. Diterpene lactone principle isolated from
white horehound, *Marrubium vulgare* (Tourn.) L., *Labiatae:*
Harms, *Arch. Pharm.* **83,** 144 (1842); Ludwig, Kromayer, *ibid.*
158, 257 (1861); Nicholas, *J. Pharm. Sci.* **53,** 895 (1964). Al-
ternate view that marrubiin is an artefact generated from *pre-*
marrubiin during the isoln: Henderson, McCrindle, *J. Chem.*
Soc. (C) **1969,** 2014. Structure and stereochemistry: Cocker *et*
al., J. Chem. Soc. **1953,** 2540; *Chem. & Ind. (London)* **1954,**
1561; **1955,** 1484; Fulke, McCrindle, *ibid.* **1965,** 647. Total
stereochemistry: Wheeler *et al., Tetrahedron* **23,** 3909 (1967);
Appleton *et al., J. Chem. Soc. (C)* **1967,** 1943. Synthesis: Man-
goni *et al., Tetrahedron* **28,** 611 (1972).

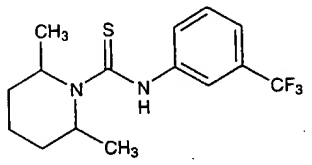


l-17β-hydroxy-19-norandrost-5(10)-en-3-one; 7α-meth-ethynyl-17β-hydroxyestr-5(10)-en-3-one; Org-OD-14; $C_{21}H_{28}O_2$; mol wt 312.44. C 80.73%, H 9.03%, O 3. Synthetic steroid with weak estrogenic, androgenic ogestogenic activity. Prepn: **NL 6406797**; H. P. de N. P. van Vliet, **US 3340279** (1965, 1967 both to Or-. Improved process: M. S. de Winter, E. A. Harryvan, **75465** (1969 to Organon). Endocrinological profile: J. ser *et al., Arzneimittel-Forsch.* **34,** 1010 (1984). Series :les on pharmacology and clinical efficacy in post-meno-women: *Maturitas* Suppl 1, 1-72 (1987). Clinical effect :oporosis: P. Geusens *et al., ibid.* **13,** 155 (1991).



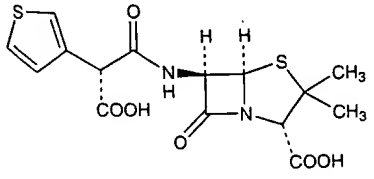
/stals, mp 165-169°.
ERAP CAT: In treatment of menopausal syndrome.

504. Ticarbodine. [31932-09-9] 2,6-Dimethyl-*N*-[3-(tri-)methyl)phenyl]-1-piperidinecarbothioamide; α,α,α-tri-)-2,6-dimethylthio-1-piperidinecarboxy-*m*-toluidide; EL-Tribodine. $C_{15}H_{19}F_3N_2S$; mol wt 316.39. C 56.94%, H %, F 18.01%, N 8.85%, S 10.13%. Deriv of thiourea, *q.v.* n: H. D. Porter, H. M. Taylor, **US 3659012** (1972 to Lilly). elmintic efficacy in dogs: R. J. Boisvenue *et al., Am. J. Res.* **33,** 709 (1972); G. F. Slonka *et al., ibid.* 1075; D. K. , J. A. Collins, *Proc. Helminthol. Soc. Wash.* **43,** 135 6).



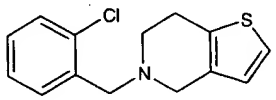
ight yellow cryst, mp 123-126°.
HERAP CAT (VET): Anthelmintic.

9505. Ticarcillin. [34787-01-4] (2*S*,5*R*,6*R*)-6-[[(2*R*)-Car-(y-3-thienylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-aza-yclo[3.2.0]heptane-2-carboxylic acid; *N*-(2-carboxy-3,3-nethyl-7-oxo-4-thia-1-azabicyclo[3:2.0]hept-6-yl)-3-ophenemalonamic acid; 6-[D(−)-α-carboxy-3-thienylacet-ido]penicillanic acid; α-carboxy-3-thienylmethylpenicillin. $_5H_{16}N_2O_6S_2$; mol wt 384.43. C 46.87%, H 4.20%, N 7.29%, 24.97%, S 16.68%. Broad spectrum semi-synthetic antibiotic lated to penicillin. Prepn: **BE 646991**; E. G. Brain, J. H. ayler, **US 3282926** (1964, 1966 to Beecham Group Ltd.). *In tro* studies: H. C. Neu, E. B. Winshell, *Antimicrob. Ag. hemother.* **1970,** 385; R. Sutherland *et al., ibid.* 390; N. J. egakis, J. Papavassiliou, *J. Antibiot.* **28,** 912 (1975). *In vivo* tudies: P. Acred *et al., Antimicrob. Ag. Chemother.* **1970,** 396. bsorption and excretion: R. Sutherland, P. J. Wise, *ibid.* 402. linical pharmacology: V. Rodriguez *et al., Antimicrob. Ag. hemother.* **4,** 31 (1973); R. D. Libke *et al., Clin. Pharmacol. her.* **17,** 441 (1975). Review of pharmacology and therapeutic fficacy: R. N. Brogden *et al., Drugs* **20,** 325-352 (1980).



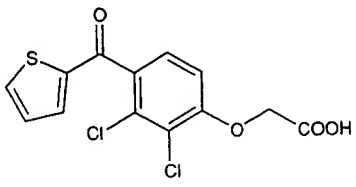
Disodium salt. [4697-14-7] BRL-2288; Aerugipen; Monapen; Ticar; Ticarpen; Ticillin. $C_{15}H_{14}N_2Na_2O_6S_2$; mol wt 428.40. Creamy-white hygroscopic non-crystalline powder. Readily sol in water (>100 g/100 ml water) giving a clear soln with pH between 6.0 and 8.0. Aq solns are relatively stable; acid solns relatively unstable (Sutherland).
THERAP CAT: Antibacterial.
THERAP CAT (VET): Antibacterial.

9506. Ticlopidine. [55142-85-3] 5-[(2-Chlorophenyl)-methyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine; 5-(*o*-chloro-benzyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine. $C_{14}H_{14}ClNS$; mol wt 263.79. C 63.75%, H 5.35%, Cl 13.44%, N 5.31%, S 12.16%. Platelet aggregation inhibitor. Prepn: **DE 2404308**; A. R. J. Castaigne, **US 4051141** (1974, 1977 both to Cent. Etudes Ind. Pharm.); E. Braye, **US 4127580** (1978 to Parcor). Metabolism: P. Godard *et al., Eur. J. Drug Metab. Pharmacokinet.* **3,** 67 (1978); *eidem, ibid.* **4,** 133 (1979); A. Tuong *et al., ibid.* **6,** 91 (1981). Mode of action: G. Leblondel, P. Allain, *Biochem. Pharmacol.* **27,** 2099 (1978); J. R. O'Brien *et al., Thromb. Res.* **13,** 245 (1978); J. J. Bruno, *ibid.* **1983,** Suppl. 4, 59. Pharmacology: A. Akashi *et al., Arzneimittel-Forsch.* **30,** 409, 415 (1980). Clinical studies: J. J. Thebault *et al., J. Int. Med. Res.* **5,** 405 (1977); C. Lecrubier *et al., Therapie* **32,** 189 (1977); T. Katsumura *et al., Angiology* **33,** 357 (1982). Review of pharmacodynamics, pharmacokinetics and therapeutic use: E. Saltiel, A. Ward, *Drugs* **34,** 222-262 (1987). Comprehensive description: F. J. Al-Shammary, N. A. A. Mian, *Anal. Profiles Drug Subs. Excip.* **21,** 573-609 (1992).



Hydrochloride. [53885-35-1] 4-C-32; 53-32 C; Anagregal; Caudaline; Panaldine; Ticlid; Ticlodix; Ticlodone; Ticlosin; Tiklid. $C_{14}H_{14}ClNS.HCl$; mol wt 300.25. Crystals from ethanol, mp 190°. uv max (water): 214, 268, 295 nm ($A^{1\%}_{1cm}$ 303.8, 13.14, 2). pKa 7.64. Almost sol in water; sol in 95% alcohol, methanol, chloroform. Insol in ether. LD_{50} in mice (mg/kg/24 hrs): 55 i.v.; >300 orally (Castaigne).
THERAP CAT: Antithrombotic.

9507. Ticrynafen. [40180-04-9] [2,3-Dichloro-4-(2-thienylcarbonyl)phenoxy]acetic acid; [2,3-dichloro-4-(2-thenoyl)-phenoxy]acetic acid; [2,3-dichloro-4-(2-thiophenecarbonyl)-phenoxy]acetic acid; tienilic acid; thienylic acid; ANP-3624; CE-3624; SKF-62698; Diflurex; Selacryn. $C_{13}H_8Cl_2O_4S$; mol wt 331.17. C 47.15%, H 2.44%, Cl 21.41%, O 19.32%, S 9.68%. A heterocyclic derivative of phenoxyacetic acid. Prepn: J. Godfroid, J. Thuillier, **DE 2048372**; **US 3758506** (1971, 1973 both to C.E.R.P.H.A.) and **FR 2115042** (1972 to C.E.R.P.H.A.). Synthesis and pharmacology: G. Thuillier *et al., Eur. J. Med. Chem.* **9,** 625 (1974). Pharmacokinetics in healthy volunteers: A. L. Kerremans *et al., Eur. J. Clin. Pharmacol.* **22,** 515 (1982). Comparative study in hypertensive patients: B. T. Emmerson *et al., ibid.* 203. Hepatotoxicity study: J. W. Manier *et al., Am. J. Gastroenterol.* **77,** 401 (1982).



Crystals from 50% ethanol, mp 148-149°; also reported as mp 157°. LD_{50} in mice (mg/kg): 225 i.v., 1275 orally (**US 3758506**).
THERAP CAT: Diuretic; uricosuric; antihypertensive.

9508. Tiemonium Iodide. [144-12-7] 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholinium iodide; *N*-